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# Vanadium in Biosphere and Its Role in Biological Processes

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**Abstract**
Ultra-trace elements or occasionally beneficial elements (OBE) are the new categories of minerals including vanadium (V). The importance of V is attributed due to its multifaceted biological roles, i.e., glucose and lipid metabolism as an insulin-mimetic, antilipemic and a potent stress alleviating agent in diabetes when vanadium is administered at lower doses. It competes with iron for transferrin (binding site for transportation) and with lactoferrin as it is secreted in milk also. The intracellular enzyme protein tyrosine phosphatase, causing the dephosphorylation at beta subunit of the insulin receptor, is inhibited by vanadium, thus facilitating the uptake of glucose inside the cell but only in the presence of insulin. Vanadium could be useful as a potential immune-stimulating agent and also as an antiinflammatory therapeutic metallodrug targeting various diseases. Physiological state and dose of vanadium compounds hold importance in causing toxicity also. Research has been carried out mostly on laboratory animals but evidence for vanadium importance as a therapeutic agent are available in humans and large animals also. This review examines the potential biochemical and molecular role, possible kinetics and distribution, essentiality, immunity, and toxicity-related study of vanadium in a biological system.

**Keywords** Metabolic role · Insulin-mimetic · Biological function · Vanadium

## Introduction

Minerals are inorganic elements, without carbon, found in small amounts in all body tissues and fluids. Although they yield no energy, minerals play an important role in many activities in the body [1, 2]. The importance of mineral elements in human, animal, and plant nutrition has been well recognized as they could be essential nutrients required for metabolic functions such as growth and development, immunity, and reproduction in both human and animals. Essential elements are ubiquitous in the environment, and its dietary deficiency results in a suboptimal biological function which is preventable or reversible by physiological amounts of the element. Minerals may be broadly classified as macro (major) or micro (trace) elements. The macro- and microminerals are required in amounts greater than and less than 100 mg/g [3], respectively. In addition to major and trace elements, small amounts of heavier elements are also present in the biological systems which are categorized as "ultra-trace" or "possibly essential elements" which include aluminum (Al), arsenic (As), cobalt (Co), chromium (Cr), fluorine (F), molybdenum (Mo), nickel (Ni), silicon (Si), tin (Sn), and vanadium (V) [4]. An ultra-trace element is one that normally comprises less than 1 μg/g of a given organism but still plays a significant role in its metabolism. These are required with estimated dietary requirements usually less than 1 mg/kg and often less than 50 μg/kg diet in laboratory animals [5]. Vanadium is believed to be important for normal cell function and development [6]. It acts as a cofactor for enhancing or inhibiting the enzymatic activity. It exists in all tissues involved in glucose homeostasis, lipid metabolism, antioxidant functions, and as an immunomodulator which has to be established in human and animals.

## Physicochemical Properties

Vanadium was discovered by Andres Manuel del Rio in 1801 in Mexico. It is classified as a transition element belonging to Group VB of the periodic table with atomic number 23, molecular weight 50.94, melting point 1890 °C, and a boiling point of 3380 °C, being the 22nd discovered element in the earth crust [7, 8] which never occurs unbound in nature. Vanadium compounds in general fall into three major categories, including inorganic vanadium salts (vanadate and vanadyl), peroxovanadium complexes, and organic V

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compounds. The average content of V is similar to that of zinc [9] constituting about 0.015% of earth's crust. The relevant forms are vanadyl sulfate, sodium metavanadate, sodium orthovanadate, and vanadium pentoxide [10]. It can exist in a variety of oxidation states − 1, 0, + 2, + 3, + 4, and + 5; the + 5 oxidation state latter being predominant under physiological conditions. The + 5 oxidation state of V exists as anionic metavanadate ($VO^{-3}$) or orthovanadate ($H_2VO^{-4}$) resembling phosphates, whereas + 4 oxidation states exist as cationic vanadyl which resembles magnesium ($Mg^{2+}$) [11]. The pentavalent ($VO^{3-}$) form predominates in extracellular body fluids, whereas the quadrivalent ($VO^{+2}$) is most common intracellularly [12].

## Occurrence

### Soil

Vanadium is ubiquitously distributed in the environment. Naturally occurring compounds which contains V are carnotite, davidite, vanadinite, roscoelite, patronite, and bravoite [8, 13]. It is concentrated mainly in mafic rocks such as basalt, gabbro (200–250 mg V/kg), shales (100–130 mg/kg), and rock phosphate, a major source of phosphorus in animal diets [14]. Wheat, rye, and red clover are indicator plants for V concentration in soil. *Cichorium intybus*, *Eupatorium capillifolium*, *Astragalus ssp.*, *Allium macropetalum*, *Castilleja angustifolia*, and *Chrysothamnus viscidiflorus* also indicate V levels in soil [15, 16].

#### Plants

Plants passively take up certain minerals from the soils that are not essential for their growth and development, but affects plants either favorably as nutrients or unfavorably as toxins. Among these are Na, I, Co, Se, Cr, Sn, F, and V that might be required by animals, but not by the plants on which they are fed. Since crops are not usually supplied with these elements, it is possible that through intensive agricultural practices, these may get depleted in the soil, thus becoming unavailable in required amounts to the animals that are fed on such plants. A lower concentration of V in soils is beneficial for plant growth and < 2 mg/kg V enhanced chlorophyll synthesis and nitrogen fixation and also facilitates utilization of potassium from the soil by the plants [17]. In another study, it was reported that < 30 mg/kg V in soil enhanced the growth of soybean but at a higher level, the shoot and roots biomass were decreased [18]. Plants are known as major V flux from soil to organisms [19] due to direct exposure, uptake, and accumulation of V in them. Vanadium concentrations in plant species vary with their leaf-stalk ratio; leaves contain higher V content than seeds and fruits [20]. It is present in vanadyl form in feeds with concentrations of less than 1 ng V/g [21]. In other natural foodstuffs also, it is present mostly in vanadyl ($VO^{2+}$) form [22]. Whole grains, seafood, meats, and dairy products generally contain 5–30 ng/g of V [23], whereas 10 μg V/kg DM [20] is present in cow's milk. Black pepper, mushroom, parsley, dill seed, cereals, fruits, and shellfish are some of the main sources of V with concentration ranging from 0.05 to 2 mg/kg [24]. Mushrooms accumulate 400 times more V than other plants [25, 26].

#### Water

Concentration of V in water varies with the geographical location and ranges from 0.2 to > 100 μg/L in freshwater and from 0.2 to 29 μg/L in seawater [27]. According to the report of WHO [28], it is present in seawater in range of 1 to 3 μg/L and in sediments from 20 to 200 μg/g. The US Department of Energy [29] documented that the accepted safe limit for V in drinking water is 0.33 mg/L. Although, WHO [30] has recommended a level of 10 μg V/L in drinking water (ranging from 1 to 30 μg/L), with an average of 5 μg V/L.

### Possible Role of Vanadium in Animals and Humans

Vanadium is a transition metal which is an endogenous constituent of most mammalian tissues. The low dose of V at cellular and subcellular levels has a potential beneficial effect [31]. Although the essentiality of V is still not clear in humans and animals, in a lower concentration, it is necessary for microorganisms, plants, and animals and its deficiency in living organisms is associated with numerous side-effects [32, 33]. V maintains plasma glucose levels by reducing its level of type 1 and type 2 diabetes mellitus lacking insulin sensitivity [34]. Also, it is reported that V alleviates cholesterol levels, heart disease, syphilis, tuberculosis, anemia, and edema, prevents cancer [34–36], and is needed for iodine metabolism and thyroid function. V salts facilitate the calcium deposition in the bones and are required for the formation of the musculoskeletal system [37] as its deficiency results into reduced growth, poor development of bone and teeth, and impaired reproductive capacity [38]. Like vanadate, decavanadate ion also interacts with major proteins such as myosin, actin, and Ca2+-ATPase, thereby affecting mitochondrial functions besides inducing changes in several cellular antioxidant markers [39]. Decavanadate increased the SOD enzyme activity, whereas no changes were reported for vanadate, but this effect largely depends on the mode of administration of decavanadate. In human beings, pharmacologic amounts of V (i.e., 10 to 100 times normal intake) affect cholesterol and triglyceride metabolism and influence the shape of erythrocytes. Besides this, it stimulates glucose oxidation and glycogen synthesis in the liver with no or slow toxicity in both normal and diabetic patients [12].

Vanadium is essential for several species of green algae (*Scenedesmus obliquus*, *Chlorella pyrenoidasa*), yellow-green algae (*Bumileriquisis filiformia*), and brown algae (*Fucus spiralis*). V-dependent iodoperoxidases in brown seaweed [40] and chloroperoxidase in the fungus *Curvularia inaequalis* [33, 41] have also been isolated and identified. Haloperoxidases, such as thyroid peroxidase, play important roles in higher animals. Diets low in iodine may amplify responses to dietary V [42].Vanadium haloperoxidases were extracted from different spp. of Laminariaceae family—*Laminaria saccharina*, *Laminaria hyperborean*, *and Laminaria ochroleuca* [43] and are classified into chloro-, bromo-, and iodoperoxidases. Vanadium chloroperoxidases (VClPOs) have only been detected in terrestrial organisms, whereas bromoperoxidases (BrPO) and iodoperoxidases (IPO) are more dominant in the marine environment. Isoforms of *L. saccharina* exhibit higher IPO and BrPO activities than *L. hyperborea*. Rehder [44] reported that VClPOs have an antimicrobial effect which is used potentially in endodontics, i.e., in the treatment of dental biofilms produced by bacterias like *Streptococcus mutans and Enterococcus faecalis*. Bromoperoxidase produced from marine algae also contribute up to 25% of the atmospheric bromine load while bromomethanes and iodine may lead to atmospheric ozone depletion and indirectly to the oxidative conversion of dimethyl sulfide and nitric oxide in the atmosphere. Recently, molybdenum-free nitrate reductase enzyme has also been isolated from bacteria *Pseudomonas isachenkovii* [45]. Vanadate under aerobic conditions is reduced to vanadyl form by cellular components such as cysteine containing peptides (glutathione), proteins, catechol, ascorbate, NADH, NADPH, and phenolic compounds [46].

The first essentiality of V in animals was reported by Hopkins and Mohr [47] in rats and chicks and is required at very low < 0.1 to 2 ppm [48] for growth in rats. It is considered essential for rats [49] as less than 100 ppb V in rat diet exhibited reduced body growth [50]. V deficiency is also associated with impaired reproduction, altered red blood cell formation, iron metabolism, and changes in blood lipid level in rats besides stunted growth [51]. It was [31, 52] reported that V deprivation in rats affected thyroid peroxidase in response to changing dietary levels of iodine.

For humans, the safe level of V intake is less than 1.8 mg/day [53]. However, the average diet can provide about 6–20 μg of V/day [54]. V salts have therapeutic properties and are recommended as dietary supplements for patients with diabetes, bodybuilders, and athletes in doses of about 60 mg/day by various National Institutes of Health [55]. V is also present in a number of multi-vitamin/mineral dietary supplements for the humans at levels of approximately 0.025 mg/day [56]. V has become a component of a large number of pills and other dietary supplements to enhance strength and treat diabetes due to its action of mimicking insulin in animal models [57]. Blood hemoglobin [58] is not affected by V deficiency; however, V-deficient diets increase the blood concentration of creatinine, triglycerides, β-lipoprotein, and the activities of enzyme-like glutamyl transferase and citrate acid cycle without altering the amino acid metabolism [59]. No reflection of toxicity after long-term supplementation of V compounds in blood was observed [60]. Keeping in view the presence of V ubiquitously, it is regarded that V could have the following physiological effects:

1. Affects glucose metabolism by acting as an insulin-mimetic agent and influencing GLUT4 translocation [61]
2. Required for osteogenic and osteoblastic activity in both growth and development [62] and bone collagen synthesis [63, 64]
3. Regulates the activity of haloperoxidase in lower forms [65], thyroid-related enzymes iodoperoxidase in higher animals [66]
4. Possess serum lipid lowering ability [67]
5. Acts as a potential antioxidant agent in diabetic conditions [68]
6. Substitutes phosphates within ATP-driven reactions [69] and interacts with Mg ion [70] in different oxidation states
7. A positive relationship with iron metabolism as important for red blood cell formation [71]
8. Plays a biochemical role in the bioavailability of Fe from milk during lactation [72] as it integrates with lactoferrin

## Absorption and Metabolism in Biological System

Vanadyl (IV; $VO^{2+}$, $V^{4+}$) and vanadate (V; $VO_4^{3-}$, $V^{5+}$) are the two most biologically stable states of V. Both the ions exist in the blood but vanadyl form predominates. Ascidians and other aquatic animals (tunicates) accumulate V in special cells known as vanadocytes. V in the blood of these organisms is more than 10 mM, whereas in the large water bodies, it is approximately 35 mM [73]. Tunicate blood cells support the accumulation of V up to million-fold concentration gradients, but since no V granules are observed in the blood cells, as V(III) exists in a reduced form that is incompatible with physiological conditions. This reduction required NADPH in the tunicate. Studies related to V uptake showed that it [74] is primarily transported to the tunicate's blood plasma via the branchial sacs [75] while some absorption also occurs via the gastrointestinal tract (GIT) where they bind to proteins, i.e., vanabins in the cytoplasm [76] which facilitates its transport and accumulation V in the vacuoles. Vanabin protein isolated previously referred to as vanadium-associated proteins (VAPs) [76, 77] are generally of three types. The isolated vanabins include proteins with apparent molecular weights of 12.5, 15, and 16 kDa [78]. Vanadocytes enter the cell cytoplasm, reduced to + 4 oxidation state by vanabins and gets

deposited in vacuoles [73, 79]. These bind V(IV) more strongly than V(V) which suggests that reduction does take place before its association with V ion [80].

The gastrointestinal and respiratory tracts are the main routes from which V is absorbed in the blood and transported to the other parts of the body as citrates, lactates, or phosphates [81] in human and animals. However, V is poorly (only about 10%) absorbed from the gastrointestinal tract [82]. Studies indicate that in animals such as sheep, V is absorbed in the upper and lower GIT, 10- and 100-fold respectively greater than those in the blood. However, in NRC [83], it has been documented that V is absorbed only less than 1%. In vitro studies suggest that V in the anionic or vanadate ($HVO_4^{2-}$) form can enter cells through phosphate or other anion transport systems [84]. Most of the ingested V is transformed into the cationic (vanadyl) form in the stomach before being absorbed in the duodenum through an unknown mechanism [85]. Dermal absorption of sodium metavanadate has also been reported through the skin [86]. Vanadate is absorbed three to five times more effectively than vanadyl [87]. The percent at which ingested V is absorbed is affected by different absorbability rates for vanadate and vanadyl, the effect of other dietary components (chromium, protein, ferrous ion, chloride, and aluminum hydroxide), on the binding and forms of V in the stomach, and the rate at which vanadate is transformed into vanadyl [88].

The level of V in human plasma is 0.42–0.08 μg/L and is excreted primarily in urine at an average concentration of 22 μg/L [89]. The major route of excretion of unabsorbed V is through feces and urine [90]. Due to low GIT absorption, dietary V is predominantly eliminated, unabsorbed via the feces. In both humans and animals, principle route of elimination for absorbed V is via the kidneys and only a minimal amount (< 10%) of absorbed V is excreted in feces. Animal studies indicated that its excretion is relatively rapid and kidney excretes about 40–60% of a dose of V within 1–3 days of absorption. In humans, daily intakes of 12–30 g V, > 5% of V is absorbed and > 0.8 g/L V is excreted in urine [88]. It was reported that effects of V administration persist even after it has been withdrawn for several days [91]. Other alternative routes of V excretion into the gut include salivary excretion or direct transfer across the intestinal wall. The skin is only a minor route of exposure for V [21].

## Distribution in Tissues

Vanadium is found in a wide variety of tissues of higher vertebrate animals, including human and is stored under normal conditions at concentrations less than 10 ng/g fresh weight [88]. Principle organs of V retention are the kidneys, liver, testicles, spleen, brain, heart, muscles, and bones. In plant and animal cells, V ranged between 10 and 20 nmol [92]. In humans, approximately, 50% of V accumulates in the bones, with the remaining part in the kidneys, spleen, liver, blood, adipose tissue, and brain [93]. Bone apparently is a major sink for excessive retained V in the body though the kidneys accumulate a larger portion of V in the body [94]. In animals, normal liver V concentrations for cattle are usually reported as 6–7 mg/kg (wet-mass basis (WM); sheep 100–220 mg/kg; dogs, 30–50 mg/kg; chickens, 18–38 mg/kg, and ducks 0.7–2 mg/kg, respectively [95]. The bone accumulates twice V than the kidney and ten times than the liver. The evidences of V storage in bone and other structural tissues in animals showed the increase in dietary V concentration from 0, 50, and 200 ppm in sheep, and bone ash V concentration also increased from 0.4 to 1.7 and 3.8 ppm, respectively [96]. Improvement in the rate of bone formation and mineralization, bone crystal length, and cortical bone toughness was found due to V supplementation. It was reported that V complexes enhanced bone formation rate, increased the osteoid volume in diabetic animals, and also reversed the harmful effects of steroidal drugs on skeletal system [97]. Sodium orthovanadate salt improved all the physical and histological abnormalities of the bone such as osteoporosis induced by glucocorticoid in the rat acting as a tyrosine phosphatase inhibitor [98].

## Distribution in Biological Fluids

The form of V in biological fluids is dependent on pH, concentration, presence of oxides as well as chelating agents [99]. V ions are conjugated with transferrin and albumin proteins in blood and are rapidly incorporated into tissues. Transferrin binds approximately 90% of the V transported in the plasma. It is not yet established whether vanadyl-transferrin complex can transfer V into cells through the transferrin receptor or whether ferritin is its storage vehicle. Transferrin has an affinity at least 10-fold greater for serum albumin than that for vanadyl cation [99]. However, serum albumin can associate with up to 20 molecules of V(IV) representing a reservoir for readily accessible V [100]. Immunoglobins have little or no affinity for vanadyl cation [101]. Less than 1% of intracellular V exists in free form where it is present as vanadyl, in association with glutathione, catacholamines, or other small peptides; while in the plasma and body fluids, it is usually bound to transferrin and in red cells to hemoglobin. Plasma V concentration is close to its physiological intracellular concentration (about 20 nM) [102], whereas total body pool of V is estimated to be about 100–200 μg [103] in humans. Its level in human blood varies widely, with increasing V levels in whole blood and in serum it ranged between 0.01 and 0.4 mg/L, approx. below 0.1 mg/L [24].

## Role of Vanadium in Carbohydrate, Lipid, and Mineral Metabolism

Role of V includes lowering of plasma cholesterol and triglycerides levels, diuretic and anticarcinogenic effect, and contraction of blood vessels and enhancement of oxygen-affinity of hemoglobin and myoglobin [57] and antidiabetic effect. It inhibits or regulates the action of receptors and non-receptor protein tyrosine kinases depending on its oxidation state [104]. It has the ability to influence enzymatic systems, namely, phosphatases, ATPases, peroxidases, ribonucleases, protein kinases, and oxidoreductases [105] and competitively inhibit activities of phosphoryl transferase enzymes in animal body thereby inhibiting $Na^+$ $K^+$ ATPase activities which regulate the $Na^+$ pump [106] and controlling the tyrosine phosphatase activity [107]. Similarity between orthovanadium and phosphate ions was reported by Crans et al. [108].

### Carbohydrate Metabolism

Among the vanadium salts, peroxovanadium (V) complexes were the first group of compounds having higher insulin activity [109]. Inorganic and organic V compounds improved glucose homeostasis in type 1 and type 2 diabetes besides having antioxidant properties in vivo conditions [101, 108, 110]. In presence of insulin, V lowers the glucose levels [111, 112] at therapeutic doses. Vanadium enhanced metabolic effects of insulin in vivo, exception being the effects on amino acid uptake, protein synthesis, and mitogenesis were not reproducible by V compounds as by insulin in diabetic animals [113] showing that only metabolic and not mitogenic effects are enhanced by V. Insulin-mimetic action of V are likely to be mediated via two pathways, i.e., insulin-dependent and independent signaling cascades to maintain homeostasis in the body. Improved insulin sensitivity in muscle cells is due to increased translocation of GLUT4 to the cell surface and not because of alterations in GLUT4 mRNA or protein expression [114]. Similarly, Trevino and co-workers [115] have reported and developed metforminium decavanadate (MetfDeca), a hypoglycemic and hypolipidemic compound by experimentation on male wistar rats with type 1 and type 2 diabetes mellitus. This has proven to provide protection on pancreatic beta cells of DM1 rats, thereby suggesting a possible regeneration of these cells by recovering their insulin levels. Therefore, MetfDeca could be considered not only as an insulin-mimetic but also as an insulin-enhancing agent. But the mechanism of action is still not clear. Similarly, a new insulin-mimetic compound hexaquis (benzylammonium) decavanadate [116] in rodent adipocytes has been reported to trigger downstream of insulin signals via insulin receptor and phosphatase inhibition, thus activating glucose transport in the complete absence of insulin [117, 118]. B6V10 [(C7H10N)6V10O28.2H2O)] is a salt conjugate of benzylamine and decavanate which acts as a substrate for vascular adhesion protein-1 (SSAO/VAP-1)/semicarbazide-sensitive amine oxidase [119]. This enzyme inhibits B6V10 and prevents lipolysis, thus leads to synergism between benzylamine and vanadate.

### Lipid Metabolism

Vanadium compounds modulate several key regulators of lipid metabolism by improving the expression of peroxisome proliferator-activated receptor γ (PPARg) and the activation of AMP-activated protein kinase (AMPK) [120, 121]. Expression of adiponectin and its multimerization are also influenced by V [122], thereby inhibiting the activity of PTP1B involved as a crosslink between signal transductions, PPARg, and adiponectin regulation, besides cooperating in insulin enhancement [123]. Several altered gene expressions involved in lipid metabolism, oxidative stress, muscle dynamics, protein breakdown and biosynthesis, the complement system, and signal transduction are also corrected by various V compounds [110, 124]. In addition, V compounds also contribute in reducing plasma triglycerides and thus preventing the development of hypertension and coronary heart disease [125]. In the STZ (streptozotocin)-induced diabetic rats, administration of both V and insulin improved lipid metabolism as monitored by plasma levels of total lipid, triglyceride, and lipogenic enzymes [126].

### Mineral Metabolism

In rats, [127] insulin along with five vanadium organic complexes, on the status of minerals such as V, Fe, Cu, Zn, Mn, Ca, and K in STZ-diabetic rat tissues, was studied. It was observed that tissue V concentration increased in vanadium-treated rats. The most pronounced influence of vanadium was observed on iron concentration in the spleen with decrease in iron concentration in the spleen while other minerals were not affected.

Vanadium influences iodine metabolism directly by affecting the thyroid gland. Role of vanadium on the iodine level was observed [31] in studies of effect of iodine to V deprivation in rats. Male weanling Wistar-Kyoto rats were supplemented with V at 0 or 1 μg/g and iodine at 0, 0.33, and 25 μg/g, respectively. Its deprivation increased thyroid weight and thyroid weight/body ratio whereas decreased the concentration of vanadium in the liver. Interaction between V and iodine was such that as dietary iodine was increased, plasma glucose increased in the vanadium-deficient rats but decreased in the vanadium-supplemented rats. Also, on increasing dietary iodine, thyroid peroxidase activity was decreased and this decrease was more marked in the V-supplemented than the vanadium-deprived rats indicating that V might have a physiological role in affecting iodine metabolism and thyroid

function. Studies on poultry [128] showed the effect of dietary vanadium on chicks fed on phosphorus-deficient diets where vanadium at 10 or 20 mg/kg in diet significantly reduced mortality rate in the phosphorus-deficient chicks. Inclusion of V in the diet resulted in increased serum phosphorus levels in the phosphorus deficient chicks. The above studies reveal that vanadium interacts with other minerals by affecting their action in the biological system.

## Pharmacological Effect

Level of V in the body varies in accordance with the consumption of iron and, thus, the level of hemoglobin in the blood is influenced as V is carried by molecules, such as those that transport iron, i.e., transferrin. It is important to maintain sodium, potassium, water, and salt balance in the body as V is also involved in the cellular mechanism of regulation of sodium pump and in maintaining normal blood pressure, reducing edema, influencing muscle and nerve tissues. V compounds are non-competitive inhibitors of $Na^+/K^+$-ATPase and mitochondrial aconitase due to their ability to bind to transport proteins [123, 129, 130]. However, $Na^+/K^+$-ATPase in vivo may be resistant to inhibition by vanadate due to the cytoplasmic reduction of vanadate to V(IV) by GSH in the cellular environment and V(IV) is a less potent inhibitor of the $Na^+/K^+$-ATPase.

Diabetic patients exhibit both abnormal glucose and lipid metabolism, which can be normalized by treatment with insulin. Studies in the animal model [9, 37] and human [131, 132] revealed that simple V salts and V complexes could also alleviate the abnormal diabetic conditions. Inorganic V compounds have a low rate of absorption compared to organic V compounds. Bis(maltolato)oxovanadium(IV) (BMOV) and bis(ethylmaltolato) oxovanadium (IV) (BEOV) are two vanadyl complexes with the VO(O4) coordination mode, which are potent glucose-lowering agents [133] as these organic compounds possess greater potency, lower toxicity, and improved tolerance ability [134].

Earlier findings suggested that V substitutes insulin in the biological system, but later it was reported that it enhances insulin action rather than replacing insulin. V ameliorates hyperlipidemia and hypertension and as counter ions for RNA, DNA, and protein in cell organelles [135] and also used in the treatment of cardiac and neuronal disorders, malignant tumors, viral, parasitic, bacterial infections (such as influenza, HIV, tuberculosis, Chagas' disease, leishmaniasis, and amoebiasis). V compounds are of concern because of its relation with the phosphate ion, its direct interaction with DNA, and its role in balancing reactive oxygen species at the tissue level. However, its role as a medicinal supplement has not been approved.

### Insulin-Mimetic Effect

The insulinotropic abilities of V salts have been pointed out in both animal and human studies. In 1899, V and its compounds were first reported as an antidiabetic agent in hyperglycemia, when dietary sodium orthovanadate ($Na_3VO_4$) reduced glycosuria in human suffering from diabetes [136]. Chronic V treatment reduced insulin requirements without affecting the plasma levels of C peptide, secreted along with insulin in equimolar concentration from pancreatic B cells, in human patients suffering from type 1 diabetes [137]. Studies on V-treated STZ-diabetic rats showed reduced insulin requirements [138]. Thus, evidence from both human and animal studies indicated the improved metabolic condition and decreased insulin requirements in diabetes.

Vanadium salts have the ability to improve insulin sensitivity in type 2 diabetes which is mainly mediated by enhancing peripheral glucose uptake thereby suppressing hepatic glucose output. In obese and type 2 diabetes mellitus rats, V improved glucose metabolism by restoring normal hepatic and skeletal muscle insulin sensitivity. In the liver, V compounds have been reported to inhibit lipogenesis [139] and gluconeogenesis [140], and stimulate glycolysis and glycogen synthesis [141]. In skeletal muscle, V augments glucose uptake [142], primarily by stimulating glycogen formation. This effect of V in restoring normal insulin and glucose levels might be due to competitive inhibition of glucose-6-phosphatase, a key enzyme in the development of insulin resistance and type 2 diabetes [143]. Oral vanadyl sulfate administered for 4 weeks @ 100–150 mg/day reduced fasting glucose in patients with type 2 diabetes [144, 145], whereas fasting glucose and HbA1c continue to reduce for 2 weeks after the end of dietary V in patients with poorly controlled type 2 diabetes [146]. Similar studies on type 2 diabetic patients on dietary sodium metavanadate regime (100 mg/day) for 12 weeks reduced levels of HbA1c, LDL cholesterol, triglycerides, and body mass index (BMI) [102].

### Mechanism of Action

Insulin-related studies on V have been mostly carried out on diabetic rats and mice where V supplementation has shown positive effects by normalizing the insulin and plasma glucose levels. In vitro studies related to rats revealed that several inorganic V compounds are similar to insulin in stimulating glucose transport and oxidation in adipocytes, increasing glycogen synthesis in diaphragm and hepatocytes while inhibiting gluconeogenesis in liver cells [147]. The mechanism behind this effect is due to the inhibition of protein tyrosine phosphatases (PTPases) enzyme intracellularly [122, 148] and activation of the insulin receptor (IR). Phosphatases have an affinity for small proteins to large receptors like the phosphorylated insulin receptor. Their mode

of action depends on the substrate and location in the cell. It was reported [149] that the limiting phosphate hydrolysis reactions are either dissociative or an associative mechanisms. PTP1B (protein tyrosine phosphatase 1B) attack the long bonds between the vanadium and oxygen atoms. Vanadium compounds inhibit all phosphatases, including those which are not even mentioned to have associative mechanism. The activation of B subunit of insulin receptor requires increased tyrosine phosphorylation [150] which occurs by preventing the dephosphorylation of the IR or activation of IR protein tyrosine kinase (PTK) which regulates down signaling of proteins for the glucose uptake and transport [130]. Potent nonselective inhibition of PTPases due to V has shown to mimic many of the metabolic actions of insulin both in vivo and in vitro. Metabolic effects of insulin are initiated by activation of its receptor on the surface of the cell leading to the activation of two main signaling cascades referred to as phosphatidylinositol 3-kinase (PI3-K) pathway and mitogen-activated protein kinase (MAPK) pathway. The PI3-K pathway is believed to mediate most of the metabolic effects of insulin, whereas MAPK pathway is mainly involved in mediating the mitogenic effects of insulin [151]. Similar to insulin, V also stimulates both glucose uptake and glycogen synthesis [152, 153]; therefore, insulin receptor and post-receptor sites have been suggested as potential sites for V action. This can be explained further as V compounds generally exert its insulin-enhancing effect through competitive inhibition of regulatory protein phosphatases, mainly protein phosphatase 1B (pp1B) which is the first phosphatase enzyme [78] in the insulin regulatory cascade particularly sensitive to inhibition by V. However, the efficiency of this competitive inhibition depends on the structure of the V complex, the oxidation state of the metal ion, and the nature of the phosphatase [74, 154, 155] thereby differing in orders of magnitude in vivo. As for example, certain V compounds such as peroxovanadate irreversibly oxidize the catalytic cysteine in protein phosphatases [155] while simple vanadate salts [156] do not undergo similar redox chemistry explained by their smaller effect on the autophosphorylation of the IR [157].

The pro-insulin-mimetic action of V involved the suppression of glucose release from the liver and kidney, inhibition of enzyme activities involved in gluconeogenesis, including glucose-6-phosphatase (G-6-Pase), phosphoenolpyruvate carboxykinase (PEPCK), and pyruvate kinase [125] besides insulin-sensitizing effects by stimulating adiponectin through a PKB-dependent transduction pathway [158]. V ions at a cellular level suggest that it behaves as phosphate analogs because of V activating protein tyrosine phosphorylation which in a mechanism similar to insulin solubilize insulin receptor causes its autophosphorylation. The second possible mechanism for its action would be regulation of activity and expression of key intracellular enzymes. Evidence from in vitro studies suggests that vanadium in millimolar concentrations activates both phosphoinositide 3-kinase and protein kinase (PKB) enzymes. V increases glucose uptake and transports from the intracellular compartment to the cell surface through the insulin-dependent glucose transporter (GLUT4) mechanism regulated by PI3K and B PKB where GLUT4 is translocated to the cell surface membrane.

GLUT4 is the major glucose transporter in muscle that is regulated by insulin. Results from the laboratory have shown that treatment of streptozotocin (STZ)-diabetic rats with BMOV, in the drinking water for 8 weeks enhanced insulin-induced GLUT4 translocation to the plasma membrane in the cardiac muscle [159]. Therefore, suggesting that V might mediate its glucose-lowering effects by enhancing glucose uptake in the insulin-responsive tissues. In vivo studies have shown that V could restore the reduced levels of GLUT4 mRNA and protein expression [160, 161] whereas it might enhance insulin-induced GLUT4 translocation from the intracellular pools to the plasma membrane in the muscle of diabetic animals [159]. But therapeutic doses of V had no effect on PI3-K or PKB activity in the skeletal muscle or liver of diabetic rats suggesting that the effects of V on GLUT4 membrane translocation are likely not mediated through PI3-K or PKB in vivo unlike in vitro conditions. Therefore, it is indicated that insulin-mimetic properties of V ions inhibit glucose release and reduce the activity of glucose-6-phosphatase involved in gluconeogenesis, accelerate transport of glucose and its oxidation, increase glycogen synthesis, attenuate lipogenesis, and inhibit lipolysis.

There are various other mechanisms of insulin-tropic action of V like reduction and increase in the expression of mRNA for neuropeptide Y (NPY) and in the level of leptin in adipose tissue respectively. Another can be the inhibition of tyrosine phosphatase receptor type 1 activity (PTP1B) that result in a loss of appetite and reduction of body weight in animal studies [4, 162, 163]. NPY was inhibited by insulin which regulates appetite and food intake.

In addition to the above, during insulin resistance in animal models, V has the ability to restore the activities of key enzymes in glycogen metabolism (glycogen synthase and phosphorylase a) and other lipogenic enzymes (malic enzyme and glucose 6-phosphate dehydrogenase) [164, 165].

### Growth Promoting Effects

Vanadium affects osteogenic and osteoblastic activity at different pharmacological doses by incorporating into hydroxyapatite lattice as it shares similar characters with phosphate ion. The compounds like oxovanadium interact with collagen and bind with the carboxylate group and glycosidic oxygen of the D-glucoronate moieties to help in cell proliferation, differentiation, and mineralization [166]. Yamaguchi et al. [167] reported that serum Ca level increased with increase in the dietary V level (15 and 20 μmol V/100 g) when dietary V

@ dose rate of 1.0–20.0 μmol V/100 g body weight as vanadium pentoxide in weanling rats. Vanadium affects mineralization in bones along with DNA content. It was reported that bone calcium content was not altered although bone DNA content and bone alkaline phosphatase (BALP) activity was increased significantly by the dose of 1.0–10.0 μmol V/100 g. A similar study also suggested that simultaneous injection of Zn as zinc sulfate (15.3 μmol Zn/100 g) for 3 days produced an appreciable increase in bone alkaline phosphatase activity, DNA, and calcium content without affecting these parameters if V (2.0 and 20.0 μmol V/100 g) was increased simultaneously. This indicates that a comparatively low dose of vanadium may play a nutritional role in the bone formation of weanling rats and that zinc might alleviate the toxic effect of V with higher doses.

### Antitumor Effect

Vanadium checks and corrects the division of cells, thereby acting as an antitumor agent. Depending on dose and type of vanadium compound used, both pro and antitumor properties are exhibited [108, 168]. Lower concentration stimulates whereas high concentration inhibits the proliferation of tumor cells [169]. Organic V compounds have less toxicity and greater bioavailability in a biological system. Vanadium induces the pro-tumor intracellular production of free radicals, leading to DNA strand breakage and chromosomal aberrations [130]. Antitumor properties of V may be due to its inhibitory effect on tyrosine phosphatase and activation of tyrosine phosphorylase enzyme [170]. Alternatively, V also inhibits tumor cell proliferation by blocking cell cycles in the G2 or M phase [168, 108]. It inhibits the generation of carcinogen-derived reactive metabolites via different pathways such as stimulating antioxidant and xenobiotic metabolizing enzymes, suppression of tumor cell proliferation, detoxifying and eliminating reactive intermediates causing apoptosis, and restricting the proliferation of neoplastic cells. A non-toxic low dose of V compounds such as VO(acac)2 (0.15 mmol/kg) is used for obtaining high-resolution images of tumor interior structures [171] pertaining to its prolonged blood half-life and selective leakage from hyperpermeable tumor vasculature.

Although V affects the glucose and lipid metabolism in a diabetic animal or human via its activation of intracellular signaling pathways, it has no effect on GLUT4 expression or membrane translocation in non-diabetic condition [159]. Again, emphasizing that V restores diabetes-induced metabolic disorders but has no effect on normal metabolism.

## Role of Vanadium in Immunity and Antioxidant Defense

The effectiveness of V compounds as immunomodulatory agents depends on its physicochemical characteristics in terms of availability, selectivity, and specificity, followed by controlled clinical trials in both human and animals. Key factors taken into consideration for immune response by V salts include (a) the nature of V itself (inorganic forms at various oxidation states, metal-organic complex species, organometallic forms, etc.), (b) the nature of ligands-substrates bound to V (e.g., peroxido, oxido, and nonperoxido organic chelators of variable O,N-containing tethers), (c) the oxidation state of V (with V(IV) and V(V) representing the well-established physiological forms in biological fluids), (d) the hydrophilicity and hydrophobicity of the ligands-substrates as well as the arising V complex inorganic-organic species, thereby allowing access to specified molecular loci of action, and (e) the binary and ternary complex metal-organic nature of vanadium. Though the need for such approaches requires exemplified and extensive research efforts in future.

Vanadium compounds are known to be involved in immune regulation and could be used as promising metallodrugs towards future immunotherapy. Vanado-drugs have the potential to influence and resensitize the immune microenvironment by interacting with immune system modulators as well as other transcription factors. It affects immune signaling pathways and activating interleukins, including IL-2, IL-4, IL-6, and IL-10 as diagnostic and immunotherapeutic tools in immunopathological disorders. The low dose of V has a positive stimulatory effect on the immune system as in mice and rats [172]. At lower doses, V regulates the immune system of the animal, affecting both humoral and cellular activities. Among all the oxidation states of V, quadrivalent salts are the most stable [173]. It is reported that B cell expands with an increase in immune response due to the proliferation of splenocytes after stimulation by V compounds [174].

### B Cell Signaling

V salts stimulate splenocytes and B cells accounting for the increased immune response [27]. It is reported that B cell expands with an increase in immune response due to the proliferation of splenocytes after stimulation by V compounds [175]. IFN- and total IgG were also amplified in splenocytes, which is correlated with the expansion of B cells although the number of $CD3^+$, $CD4^+$, and $CD8^+$ cells of splenocytes remains the same. V affects mitogenic responses in lymphocytes by interacting with T and B cells in a distinctly different manner, thus modulating B cell immune response [27]. Studies revealed that not only action and effects of insulin are mimicked by V treatment in diabetic animals but also B cell lesions are partial, prevented, or treated by V salts on dietary administration [42]. Studies revealed that not only action and effects of insulin are mimicked by V treatment in diabetic animals but also B cell lesions are partial, prevented, or treated by V salts on dietary administration [176].

### T Cell Signaling

Similarly, V also activates T lymphocytes that play a central role in cell-mediated immunity and are characterized by the presence of a T cell receptor (TCR) on their cell surface [177]. V alters CD4+ T helper (Th) cell expression, serving as an important initiator and regulator of cellular and humoral immune responses against infectious microorganisms and other antigens. Like other metals, V has been found to interact prooxidatively with cells of the innate immune system, including neutrophils, macrophages, basophils, as well as epithelial cells [178]. The exposure of activated human neutrophils to V (25 μM) in the + 2, + 3, and + 4, but not the + 5, valence states promoted hydroxyl radical formation by these cells [179] due to an interaction of the metal via Fenton reaction. Though this mechanism may be of greater relevance to macrophages as these cells do not possess the enzyme myeloperoxidase thus neutralizing the competition between the metal and the enzyme for $H_2O_2$ [180]. V might have the function on intestinal mucosal immunity by affecting the pathways that reduced the lymphocyte population or lymphocyte activation. Dietary administration of 5 and 15 mg/kg V as ammonium metavanadate in day-old avian broilers showed no effect on the number of cytokines in the intestinal mucosa [181] whereas mRNA expression of Toll-like receptors such as TLR4 and TLR7 in lymphoid organs was up-regulated with decreased immunity if more than 30 mg V/kg was administered in the diet [110]. Expression of CD3+, $CD3^+CD4^+$, and $CD3^+CD8^+$ T cells in both ileac lamina propria lymphocytes (LPLs) and intraepithelial lymphocytes (IELs) were also influenced by vanadium. Enzymes such as kinases, GTPases, and transcription factors [182] result in changes in cell metabolism, gene expression, and cytoskeletal organization which was affected due to V supplement. Furthermore, this V also influences cellular mechanisms such as survival, tolerance, apoptosis, proliferation, and differentiation into antibody-producing cells or memory B cells. V affects the growth and proliferation of microorganisms by inhibiting mevalonate kinase enzyme which might be the possible reason of slowing down the growth of bacteria, especially gram-positive bacteria, as mevalonate kinase is present in their isoprenoid biosynthesis pathway [183], but its impact on higher animals is still a topic to be looked into. T cells are essential for immunity for every aspect of the adaptive immune response, and their signaling is regulated by V due to change in the number of mature cells migrating from the thymus to the spleen which in turn affect secretion of IL-2 and IL-6. Upregulation in the systemic concentrations of inflammation-related cytokines such as IL-6, IL-8, IL-18, TNF- (tumor necrosis factor alpha), and C-reactive protein (CRP) [168] are the characteristics of inflammatory reactions. The inflammatory cascade is activated by immune cell mediators, transcription factors, and chemokines [184]. In this support, evidence revealed that V could down-regulate inflammatory reactions both in vitro and in vivo [42]. Hepatoprotective action of V is indicated by the reduced levels of serum creatinine and blood urea nitrogen suggestive of an ameliorative effect of V salts on renal dysfunction [185]. Neuroprotective properties of V [186] was confirmed by the activity of bis (peroxido)vanadium (Bpv), a specific inhibitor of PTEN's phosphatase which significantly increased IL-10 levels and decreased TNF- concentration in the ischemic boundary zone of the cerebral cortex. Though PTEN mRNA and protein levels were reduced but PI3K, Akt, and p-GSK-3휁 protein expression were increased in the ischemic boundary zone of the cerebral cortex on vanadium (III)-(L-cysteine) treatment [42].

### Antioxidant System

Vanadium contributes to antioxidant system improving the oxidative status and reducing free radicals by scavenging superoxide anion, hydroxyl radical, and intracellular reactive oxygen species via inhibition of lipid peroxidation. Thus, it has the potential of restoring the imbalances in the antioxidant system and plasma enzymes which are responsible for the cell dysfunction and destruction. Benefits to scavenge free radicals suggest its ameliorative potential against oxidative stress as it efficiently increases cellular GSH level and also up-regulates mRNA and protein expression of a catalytic subunit of glutamate cysteine ligase (GCLC), which is involved in glutathione (GSH) synthesis [187]. Vanadyl sulfate given @ 100 mg/kg body weight for 60 days in male albino rats reduced the elevated activities of GR, GPx, and GST in the diabetic group [188] and increased plasma GSH levels in obese rats [69]. Lower doses of V complex increased the activity of glutathione peroxidase thus alleviated the effect of reactive oxygen species in the diabetic animals. This improvement in GPx activity might be the action of V in increasing the nuclear translocation and accumulation of phosphorylated Nrf2 which led to amplifying in expression and activity of glutathione peroxidase as reported in human liver cells in vitro [187]. Supplementation of vanadyl sulfate (0.2 mg/ml in drinking water for 7 days) protected diabetic rats from lipid peroxidation as TBARS (thiobarbituric acid reactive species) were also influenced on supplementation of vanadyl sulfate [175].

Oxidative stress in diabetes is involved in both the origin of the disease and increasing secondary complications [189] resulting in the production of free radicals, especially in the pancreas, which is a major cause in the development of insulin resistance in both type 1 [190] and type 2 diabetics [56]. Beneficial or toxic effects of V, in case of insulin sensitivity, are based on its redox regulation in vivo. V corrects and improves glutathione peroxidase, catalase, and superoxide dismutase levels to near normal values in stress conditions such as diabetes. This property of V is supported by findings in the obese rats where oxidative stress was potentially reduced on

dietary supplementation [191] and is known to decrease oxidative damage remarkably in the diabetic heart [192, 193] in rats. Unlike insulin, V is only partially able to control the impaired antioxidation system of diabetic rats.

### Toxicity of Vanadium

Despite positive effects of vanadium on various mechanisms, its too high concentration in an organism can disrupt the main functions of the organs. The dose of V is important as it differentiates between a remedy and poison. Generally, V toxicity occurred via two distinct pathways; one is dependent and the other is independent of $H_2O_2$ production, which could be blocked by either catalase or glutathione peroxidase [194]. Studies on rats depicted no toxic effects at therapeutic doses of V [195]. However, at higher doses, toxicity was observed due to the inhibition of oxidative phosphorylation [89]. Toxicity of V in animals depends on various factors, such as the type of compounds, the degree of oxidation, dose and time of administration [103], which rises with increasing oxidation state; hence, + 5 oxidation state of vanadium is the most toxic [89]. Organic V compounds are safer to use in animals [126] than inorganic salts. Signs of V poisoning in humans are heart palpitations, exhaustion, depression, trembling fingers, and hands, affecting respiratory and digestive system with a characteristic green tongue [196]. It was reported that acute systemic toxicity of V impaired oxidative metabolism with suppression of enzymes and respiratory processes in cells and pathological changes within the kidneys, such as degeneration of the renal tubules, congestion in the liver, and inflammation in the intestinal cells [196]. It has been reported that high doses of V can be teratogenic and can lead to lipid peroxidation [197, 198]. Gastrointestinal symptoms, including diarrhea, vomiting leading to dehydration, and weight reduction [199] in humans have also been observed. Other examples showed that salts of V, including, vanadium chloride, vanadyl sulfate, and meta- and orthovanadate (9.2 mg/kg of vanadium for each compound) significantly reduced the number of red blood cells (RBC) in humans inducing peroxidative changes and deformity in erythrocyte membranes, resulting in hemolysis and shortened RBC survival when administered in high doses [200, 201].

Genotoxicity by V compounds has been mainly exhibited in the + 4 and + 5 oxidation states, resulting in an occurrence of chromosomal aberrations, DNA strand breakage, and hydroxylation of guanosine thereby, causing the generation of free radical production [202, 203]. Mitochondrial functions were mostly affected by V compounds where oxidative stress induced in mitochondria caused PTP opening, leading to the collapse of mitochondrial transmembrane potential (DWm) and cytochrome c (Cyt c) release initiating cell apoptosis as observed in rat livers [110]. Although in animal studies, decavanadate was found to be a more potent mitochondrial depolarizing agent and a more potent inhibitor of mitochondrial oxygen consumption than monomeric vanadate [204].

## Conclusions

The omnipresence of vanadium in feeds and drinking water and similarity with phosphate and magnesium ions suggest that V also attains a general role in life by influencing on metabolic processes. Functional V compounds have been found important in lower forms of life as V nitrogenases and vanadate-dependent haloperoxidases. It has potential for improving type 1 and 2 diabetic conditions in humans and acts as an antitumor agent and has positive effects on T cells and B cells activity. However, the safe dose of vanadium is still a controversial and the too high concentration of the mentioned element can lead to many various pathological alterations within the organism as it can affect the activities of intracellular enzyme systems and modify physiological processes like digestion, respiration, etc.

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